prosecution. No new matter is believed to have been added and entry of the amendment is again respectfully requested.

It is respectfully requested that the drawing corrections be held in abeyance until the application is in condition for allowance.

Claims 1-5 are rejected under 35 USC 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants respectfully traverse.

Claim 1 now recites the steps the Examiner urged to be essential and missing. To the extent the rejection was based on the failure to recite these steps, it should be withdrawn.

With regard to the perceived breadth of the claim element "transgenic non-human mammalian or avian host", the claim has been amended to delete reference to avian and the transgenic non-human mammalian species have been limited to those that express at least one human HLA antigen. The sole function of the transgenic non-human mammal is to produce HLA restricted cytotoxic lymphocytes when challenged with an appropriate dose of TAA. This immunological challenging event is not one which would be taken as requiring an unacceptable level of experimentation. More importantly, the Examiner has not established this immunological response event as one which would be associated with undue experimentation. The transgenic employed by Applicants was merely an "off the shelf " reagent and not one created to accomplish the invention. The creation of a novel transgenic is not part of the disclosed inventive contribution.

Accordingly, the state of the art of transgenics at the time of filing the application should not be an issue here. If an existing transgenic or one which later comes into existence meets the claim definition it is suitable for Applicants' purposes. The transgenic is merely a "reagent" which upon challenge produces a source of HLA restricted CTLs.

The cited references do not detract from this. Wall, *et al.* (1996, Theriogenology, Vol. 45, page 57-68) and Ebert, *et al.* (1988, Mol. Endrocrinology, Vol. 2, pages 277-283) merely show the unpredictability of transgene behavior may be due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression. Overbeek's reference (1994, "Factors affecting transgenic animal production," Transgenic Animal Technology, pages 96-98) merely shows that within a litter of transgenic mice, there is

variation in the level of transgene expression occurs between founder animals and results in different phenotypes.

The fact that integration of the transgene into the transgenic animal genome is a random event does not detract from the acceptance of screening as a tool in this art to isolate operable reagents. One merely uses screening to identify a transgenic animal wherein the transgene has integrated into a site that provides reasonable expression and stability of the gene. For example, Damak, *et al.* (Biotechnology (NY) 1996 14; 185-188) demonstrated improved wool production using a transgenic sheep using screening techniques. A refined method for generating transgenic pigs was discussed by Piedra, *et al.* (J Reprod Fertil Suppl 1997 52; 245-254), and a transgenic goat producing human anti-thrombin III was constructed (USP#5,843,705). These discoveries resulted in part from the use of screening techniques. It is clear that non-human transgenic mammals have been made successfully by various laboratories. In addition, transgenic goats which produce antibodies in milk have also been created (USP#5,827,690). Since HLA molecules belong to the antibody superfamily, it is likely that genes encoding for the HLA molecules can be successfully implanted into non-human mammals such as goat, cow and pig with an expectation of the successful establishment of HLA transgenic animals.

With regard to the Examiner's assertions regarding the infancy of the transgenics field and the associated claim scope issue, please note that there are an increasing number of transgenic successes. For example, Taurog, *et al.* (J Immunol 1988 141; 4020-4023) described the construction of HLA-B27 transgenic mice and Ito, *et al.* (J Exp Med 1996 183; 2635-2644) described the generation of HLA-DR4 transgenics. Accordingly, the evolving field has associated with it a trend where there is an expectation of success associated with the construction of other nonhuman mammalian transgenics like the disclosed transgenic mice carrying any HLA gene without a perception that there would be always be a need for the exercise of inventive efforts.

Also note that the disclosed invention involves T Cell receptors from the HLA-restricted, antigen-specific CTLs. This too is more common place. Taurog, *et al.* (J Exp Med 1994 180; 2359-2364) worked with HLA-B27 transgenic rats to study inflammatory diseases, and Kawamura, *et al.* (J Clin Invest 2000 105; 977-984) described the use of HLA-DR2 transgenic to study human CNS autoimmune disease. In these cases, T cells are responsible for the initiation of the autoimmune diseases in the transgenic animals. This further demonstrates that HLA

transgenic mice upon immunization are excellent reservoirs of HLA-restricted antigen specific T lymphocytes. Collectively taken, the art does not support the notion that patent claims should be limited to only HLA-A2. Many of the references cited above describe transgenic mammals that express various HLA molecules, not just HLA-A2. Therefore, undue experimentation at the time of the patent filing was not necessary to demonstrate the creation of transgenic mammals with other HLA molecules. Based on the literature at the time of filing, various HLA expressing transgenic mammals were available for use as a tool in the method claimed in this patent application.

Accordingly, it should be noted that a proper prima facie case regarding "undue experimentation" as to each of the items enumerated by the examiner has not been made. Further, It is not clear from the record why extrapolating from the core materials, steps and conditions found by the Examiner to be enabled to "known" equivalents cover by the claims would involve anything more than routine trial and error experimentation. Mere assertion of claim breadth or infant technology field does not establish undue experimentation.

Claims 1-5 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse.

The claims have been amend to address the points raised in the Official Action.

Withdrawal of the rejection is respectfully requested.

Claims 1-5 are rejected under 35 USC 103(a) as being unpatentable over Man *et al.* in view of Cole *et al.* Applicants respectfully traverse.

Here, both the references, taken alone or in combination, fail to teach elements clearly required by the claims, *e.g.*. transgenic mouse, *etc.* The Examiner merely asserts that the inclusion of the missing elements and their interchangeability would be obvious. The cited art fails at the outset to factually establish a proper prima facie case of obviousness.[1] Further, while

[1] The Examiner notes one of the deficiencies of Man, *et al.*- Man et al. does not teach using the transgenic mouse to identify tumor associated antigens. The reference also clearly does not teach all the elements needed to create a transgenic mouse that could be used in that fashion.

the references teach specific technologies, it is not clear from looking at the reference why their combination would have been suggested or whether the requisite guidance and motivation exists which would cause one skilled in the art to make the requisite changes to arrive at the invention as claimed.

Man, *et al.* (1994, J. Immunol., Vol. 153, page 4458-4467) teach the use of influenza A antigen, M1, to immunize transgenic mice carrying the HLA-A2.1 transgene and obtained cytotoxic T cells which recognize the M1 antigen. They analyzed the Vα and Vβ of the antigen-specific TCRs by PCR using class specific primers, but did not the TCR genes. Further, Man, *et al.* does not teach using the transgenic mouse to generate cytotoxic T cells against tumor associated antigens. At the time of filing, a number of tumors associated antigens and certain epitopes of these tumor-associated antigens, presented by HLA-A2 molecules, had been identified.

Cole, *et al.* (April 1995, FASEB Journal, Vol. 9, page A801, abstract 4638) demonstrate that HLA-A2 restricted cytotoxic T cells could be isolated from human patients against the melanoma associated antigen Mart-1. The success of generating cytotoxic T Cells against certain epitopes of tumor-specific antigens in HLA-A2 humans cannot reasonably predict the success of generating cytotoxic T Cells against identical epitopes in the HLA-A2 transgenic mice. This is due to the difference in substrate specificity of molecules involved in the antigen processing and presentation pathway between humans and mice. For example, the major cytosolic protease responsible for the production of antigenic peptides is the proteasome in humans and mice. Cytosolic peptides are delivered to the endoplasmic reticulum by the transporter associated with antigen processing (TAP). To be efficiently transported, peptides must be between 8 and 16 residues long and have the proper COOH-terminal residues. Mouse TAP prefers a hydrophobic residue, whereas human TAP prefers a hydrophobic or positively charged residue (see page 55 in J. W. Yewdell and J. R. Bennink, 1999, Annu. Rev. Immunol 17:51-88). These preferences match those exhibited by mouse and human class I molecules for COOH-terminal residues. Therefore, it is conceivable that the same antigen, such as a human tumor associated antigen, might be processed differently in each antigen-processing pathway generating pools of peptides that are significantly different in amino acid composition between humans and mice. As a result, immunogenicity of antigens might change substantially from humans to mice. It is also known that immune responses to particular antigens could be

considerably different among individuals. For instance, studies have shown that patients infected with HIV-1 exhibit a high degree of variation in their population of cytotoxic T cells against the virus (Barton et al., 1996, Science 271:324-328). Therefore, it would not have been obvious to one of ordinary skill at the time of the invention to use the method of isolating TCR genes from transgenic mice taught by Man, *et al.* to obtain TCR genes specific for tumor-associated antigen, such as Mart-1.

In addition, the stated and apparent rationale for the finding of obviousness appears to be based on an obvious to try rationale. The certainty of a successful outcome at the level requisite for statutory obviousness are not evident from the record.

The additional references are cited. These references merely show the existence of additional elements. The mere existence alone does not suggest its combination with others to arrive at an invention not envisioned by any of the references.

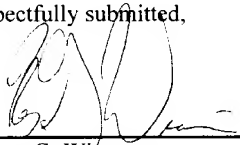
Since a proper prima facie case of obviousness has not been established, withdrawal of the rejection as stated is respectfully requested.

Having addressed all of the objections and rejections, the application is believed to be in condition for allowance and a notice to that effect is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 313332000100.

However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,



Dated: November 30, 2000

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